



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,758	10/23/2000	Shukti Chakravarti	CWV-001.01	7408

41552 7590 10/23/2006

MCDERMOTT, WILL & EMERY  
4370 LA JOLLA VILLAGE DRIVE, SUITE 700  
SAN DIEGO, CA 92122

EXAMINER
----------

LIU, SUE XU

ART UNIT	PAPER NUMBER
----------	--------------

1639

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/694,758	CHAKRAVARTI, SHUKTI	
	<b>Examiner</b>	<b>Art Unit</b>	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 August 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 42-52 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 42-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/14/05</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Claim Status***

1. Claims 1-41 have been canceled as filed 11/15/05;  
Claims 42-52 have been added as filed 11/15/05;  
Claims 42-52 are currently pending and are being examined in this application.

### ***Election/Restrictions***

2. Applicants elected Group IV (original Claims 5-7), and MMP-12 for the species of a gene, as acknowledged in the previous Office action mailed 7/30/02, p. 2. Applicant's newly added claims (the pending claims 42-52) read on the originally elected Group of invention, and thus are examined in this application.

### ***Priority***

3. This application claims priority to U.S. Provisional Patent Application No. 60/160,835, filed 10/21/1999.

### ***Claim Rejections Withdrawn***

4. In light of applicants' cancellation of Claims 30-41 (claim amendment filed on 11/15/05), the following claim rejections as set forth in the previous Office action (mailed 6/14/05) are withdrawn:

A.) Claims 30-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not

Art Unit: 1639

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

B.) Claims 30-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

C.) Claims 30-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

D.) Claims 30-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp 660-669) and Poulakkainen (G4358), and Prehn et al (G4355) (Gastroenterology, vol 114, No. 4, April 1998) and further in view of specification disclosure.

E.) Claims 30-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol 114, No. 4, April 1998) and Poulakkainen (G4358).

F.) Claims 30-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol 114, No. 4, April 1998) and in view of specification disclosure.

However, the newly added claims (Claims 42-52) are drawn to the same invention as the originally examined claims (Claims 30-41). Thus, the written description rejections and the art rejections still apply to the newly added claims as discussed below. Applicants' traversal over the previously set forth rejections that are applicable to the new rejections are addressed below as well.

### **Maintained Rejections Over Newly Added Claims**

#### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

6. Claims 42-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

The instant claims recite a method for determining an inflammatory bowel disease (IBD) or pre-IBD phenotype of a test cell from a given tissue, said method comprising: (a) determining an expression level of at least one gene product in said test cell, wherein said gene product is an mRNA of a gene selected from the group consisting of macrophage inflammatory protein-2/3 (GRO3), neutrophil lipocalin (HNL), macrophage elastase (MMP-12), elastase specific inhibitor (elafin), and type VI collagen  $\alpha$ 3 chain (COL6A3); and (b) comparing the expression level of said gene product in said test cell to an expression level of said gene product in a control cell of the given tissue type, wherein a difference in the expression level of said gene product indicates that said test cell has an IBD or pre-IBD phenotype.

*To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.*

*Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565; 19 USPQ2d at 1118.*

*The written description requirement of 35 U.S.C. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).*

*With regard to the description requirement, applicants' attention is invited to the decision of The Court of Appeals for the Federal Circuit, which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].*

*The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or*

*disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.*

The instant specification and/or the aforementioned claims do not provide adequate written description to show possession of the entire genus of IBD. IBD encompasses a variety of diseases with different symptoms and clinical manifestations as taught by, for example, Robbins et al. (Pathologic Basis of Disease, 2<sup>nd</sup> ed., 1979, Page 958 and Page 982). The instant specification and/or claims do not provide an adequate number of representing species of the different diseases. It is not clear in the instant specification or claims that the claimed probes for the different genes can be used for monitoring gene expression in all inflammatory bowel diseases. For example, a specific gene might be overexpressed compared to the control sample in one type of IBD, but may be normally expressed in another type of IBD. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The instant claims are drawn to a method for determining the gene expression level of at least one gene in a sample. The instant claims further recite using array to determine the gene expression levels. However, the instant specification does not provide adequate written description to show possession of the claimed method of determining gene expression using DNA array comprising nucleic acid probes to determine IBD in cells. The instant specification defines the term “microarray” as “an array of distinct polynucleotides or oligonucleotides synthesized on a substrate...” (p. 15, lines 30+ of the spec.), which is interpreted to mean that the DNA microarray contains nucleic acids with defined sequences. However, neither the instant

Art Unit: 1639

specification nor the claims specifically recite nucleic acid probes that constitute the claimed array. Claims 42-52 recite a method of determining expression levels of at least one gene from the 5 listed genes (i.e. GRO3, HNL, elafin, COL6A3, and MMP-12) using DNA array with specific nucleic acid probes. The said "nucleic acid probes" could be different DNA molecules such as cDNA of the claimed genes, or short oligomers that are complementary to either the coding strand or the complement strand. The probes could also contain mutations relative to the wildtype gene sequences. The probes could even be complements to genes that regulate the said 5 genes. In addition, the probes could also have various lengths or sequence segments within the claimed gene sequence. These different variables together would create almost infinite combinations of different probes that could be encompassed by the claimed array of the probes.

Furthermore, the instant claims and specification only define the specific genes by their GenBank accession numbers. The specific sequences for the probes that can hybridize to these genes are not provided. In addition, the GENBANK accession number do not provide a reference to a stable, know and non-changing source of information. GENBANK information may be updated and revised anytime (see <http://www.ncbi.nih.gov/Genbank/index.html> (2006) under the heading Updating or Revising a Sequence), therefore, the sequence for the claimed genes could change anytime. A person of ordinary skill in the art would not be able to envision that the applicants had possession of the recited invention as described. It is unclear as to what portion of the gene sequences are used, or suitable for the said probes for the array.

Discussion and Answer to Argument

7. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue that the specification has support for determining gene expression levels of samples from subjects, and indicating the subject has IBD or is at risk of developing IBD (Reply 11/15/05, p. 5, para 2).*

Applicant's argument is based on limitations not found in the instant claims. The instant claims are not drawn to a method of diagnosing IBD in a subject.

*Applicants state that the instant specification provides GenBank accession number for each of the claimed genes (Reply 11/15/05, pp. 5-6)*

Applicants' arguments are addressed by the above Written Description rejection.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 42-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

Claims 42-52 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: A.) determination of a test cell or a tissue that has

Art Unit: 1639

inflammatory bowel disease (IBD) or pre-IBD; B.) the specific method steps for determining the gene expression levels of the listed genes in the instant Claim 42; C.) the method steps for comparing the different expression levels of the said genes, and which comparison results would allow the determination of the phenotype of the cells. The instant claims (especially Claim 42) is reciting a method of “determining an inflammatory bowel disease (IBD) or pre-IBD) phenotype of a test cell from a given tissue” in the preamble, which indicates that the phenotype (having IBD or not) of the “test cell” is not necessarily known. However, the instant claimed method steps (Claim 42) require that the phenotypes (disease state) of the “test cell” and the “control cell” from the give tissue are known, and thus the gene expression levels from these cells can be compared. This apparent contradiction of the instant claims renders the claims indefinite.

Claim 42-52 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the specific relationship between each of the listed gene expression level and the IBD phenotype of the test cell. It is not clear how the various expression levels of the different genes are related to the determination of the inflammatory bowel disease of a cell. It is also not clear how the comparison of the gene expression levels between the disease cell and the control cell relate to the disease state of the cells. It is further not clear how the gene expression levels distinguish between UC and CD.

Claim 46 recites the phrase “the expression level of said gene product differs by at least a factor of two”, which is not clearly defined. It is not clear from what the said gene product’s

Art Unit: 1639

expression level is to differ. The specification and the claims also do not clearly define the term (“at least by a factor of two”) that used to measure the differences.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited), and Poulakkainen (G4358; previously cited). This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

The instant claims recite a method for determining an inflammatory bowel disease (IBD) or pre-IBD phenotype of a test cell from a given tissue, said method comprising: (a) determining an expression level of at least one gene product in said test cell, wherein said gene product is an mRNA of a gene selected from the group consisting of macrophage inflammatory protein-2/3 (GRO3), neutrophil lipocalin (HNL), macrophage elastase (MMP-12), elastase specific inhibitor (elafin), and type VI collagen  $\alpha 3$  chain (COL6A3); and (b) comparing the expression level of said gene product in said test cell to an expression level of said gene product in a control cell of the given tissue type, wherein a difference in the expression level of said gene product indicates that said test cell has an IBD or pre-IBD phenotype.

**Alexander** et al, throughout the publication, disclose a method to determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD), which reads on the determining gene expression of **clm 42**. The reference assayed transcripts of 15 protooncogenes (refer to IBD genes) in colonic epithelial cells of IBD patients and controls (e.g., see abstract). The reference discloses that increased levels (refers to the differential expression of the instant claim) of soluble mediators (e.g. Leukotrienes, prostaglandins) of inflammation as well as the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (e.g., see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (i.e., see left column in page 661). These read on the comparison step of **clm 42**.

The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about two fold higher than in the uninvolved IBD samples, which reads on the at least a

Art Unit: 1639

factor of two difference in expression level of **clm 46**. The reference also teaches cells obtained from patients with UC and CD (Abstract of the reference), which reads on the IBDs of **clms 43 and 44**. The reference also teaches that certain genes expression levels are different in UC when compared to CD patients (Abstract of the reference), which reads on the distinguishing between UC and CD step of **clm 45**.

The reference also teaches samples are obtained from surgery (p. 661, right col., para 2), which reads on the sample of **clm 47**. The reference also teaches hybridization analysis (e.g. northern blotting) to analyze gene expression (p. 662, right col.), which reads on the method step of **clm 48**. The northern blotting membrane also reads on an array having a substrate (**clms 49-52**), because the northern blotting membrane has probes bound thereto and the probes are arranged in a two dimensional matrix format (see Figure 2 of the reference).

Overall, Alexander et al teach a method to determine the differential expression of genes involved in IBD.

Alexander et al do not specifically teach the five listed genes in the instant **clm 42**. However, the genes in listed in the instant Claim 42 (and Table 1 of the instant specification) are not novel genes, and are well known for their role in IBD. The specification in page 19, discloses 'Table 1 indicates those sequences which are over- or underexpressed in a CD- or UC-derived cells relative to normal tissue.' Applicants in the specification disclose the GenBank accession numbers of the genes used in the claimed method. Thus, all the genes used in the claimed method are well known in the art.

**Puolakkainen** et al (G4358), throughout the publication, teach distinct expression profiles of stromelysin-s, collagenase and MMP-12 in intestinal ulcerations. As taught by

Art Unit: 1639

Alexander et al, Crohn's disease (CD), and ulcerative colitis (UC) are part of larger group of IBDs (p. 660 of Alexander).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use all the known genes involved in IBD and use the genes (or probes) in array format to determine the IBD or pre-IBD phenotype.

A person of ordinary skill in the art would have been motivated to use all the known genes or genetic markers involved in IBD in an array format to screen IBD cells, such that the efficiency of the method improves (i.e., more markers used the more different mechanisms involved in IBD are determined). Because Alexander et al teach that the genes that are differentially expressed in IBD patients can be used as markers for development of colon cancer in IBD (Abstract, last lines), a person of ordinary skill in the art would have been motivated at the time of the invention was made to use the differentially expressed MMP-12 (as taught by Puolakkainen et al) as a gene marker for determining IBD phenotype of cells.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for monitoring gene expression such as using DNA microarray and the specific genes (such as MMP-12) are known in the prior art such as taught by Alexander et al and Puolakkainen et al, who have demonstrated the detection of expression of various genes in IBD cells.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue that the instant claims (especially Claim 42) "recites a method for diagnosing IBD in a subject" (Reply entered 11/15/05, p.7, para 1).*

Contrary to applicant's statement, the instant claims are not drawn to a method of diagnosing IBD in a subject. The instant claims recite a method of determining the expression level of genes from cells of a given tissue type.

*Applicants argue that the rejections over the combination of Alexander and Poulakkainen references do not teach any of the claimed genes in the instant Claims (i.e., GRO3, HNL, elafin, or COL6A3) (Reply entered 11/15/05, p.7, para 2).*

The instant claims (Claim 42) lists five specific genes including GRO3, HNL, elafin, or COL6A3, and MMP-12, which the MMP-12 gene is the elected species of gene as discussed supra in the Election/Restrictions section of the instant Office action. As discussed above and pointed out by the applicants (Reply entered 11/15/05, p. 7, para 2), Puolakkainen et al teach MMP-12 gene is differentially expressed in IBD cells.

*Applicants also argue that the genes listed in Table 1 (including GRO3, HNL, elafin, or COL6A3, and MMP-12) of instant specification are not known for their roles in IBD (Reply entered 11/15/05, pp. 7-8, bridging para).*

As discussed above, the MMP-12 gene is known to be differentially expressed in IBD cells as taught by Puolakkainen et al.

14. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol 114, No. 4, April 1998; cited previously) and Puolakkainen (G4358; cited previously). This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

**Dieckgraefe** et al, throughout the publication, disclose a method for identifying gene expressed in IBD, which reads on the determining gene expression of **clm 42**. The reference has used GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohns' disease, and both in inflamed and non-inflamed non IBD specimens (Background section of the reference), which reads on the UC and DC of **clms 43 and 44**. The reference also teaches RNA isolated from the mucosa of colonic resection specimens was used to generate hybridization probes (See Methods), which reads on the surgical resection sample of **clm 47**. The reference also teaches light directed solid-phase combinatorial chemistry was used to generate oligonucleotide probe array (see Methods), which reads on the nucleic acid probes, array, and substrates of **clms 48-52**. The reference in the results section discloses that dramatic changes were seen in the expression of wide range of genes, genes were identified which appear to be specific markers for the specific diagnosis, disease activity and specific feature of

Art Unit: 1639

histology, and specific genotype diagnosis for UC group, which read on the step of distinguishing between UC and CD of **clm 45**. The reference also teaches dramatic changes of gene expression for a wide range of genes (Results section of the reference), which reads on the at least a factor of two difference in expression of **clm 46**.

Dieckgraefe et al also teach the need to identify gene markers differentially expressed in CD and UC, and the need to use different genes that are differentially expressed to identify genotypes for the different diseases (such as CD and UC) for potential pharmaceutical purposes (see Aims section of the reference). The reference further teaches host defense molecules are over expressed in IBD cells (Results section).

Dieckgraefe et al do not explicitly teach using MMP-12 as a gene marker for IBD determination.

However, the genes shown in Table 1 (which comprises MMP-12) of the instant specification are publicly known and available. Furthermore, **Puolakkainen** et al, throughout the publication, teach distinct expression profiles of stromelysin-s, collagenase and MMP-12 in intestinal ulcerations.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention to use all the known genes involved in IBD and use the genes (or probes) in array format to determine the IBD or pre-IBD phenotype.

A person of ordinary skill in the art would have been motivated to use all the known genes or genetic markers involved in IBD in an array format to screen IBD cells, such that the efficiency of the method improves (i.e., more markers used the more different mechanisms involved in IBD are determined). Because Dieckgraefe et al teach the need to identify gene

Art Unit: 1639

markers differentially expressed in different diseases such as UC and CD for potential pharmaceutical purposes, and many host defense molecules are over expressed in IBD cells, a person of ordinary skill in the art would have been motivated at the time of the invention was made to use the differentially expressed MMP-12 (as taught by Puolakkainen et al) as a gene marker for determining IBD phenotype of cells.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for monitoring gene expression such as using DNA microarray and the specific genes (such as MMP-12) are known in the prior art such as taught by Dieckgraefe et al and Puolakkainen et al, who have demonstrated the detection of expression of various genes in IBD cells.

*Discussion and Answer to Argument*

15. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue that the instant claims (especially Claim 42) "recites a method for diagnosing IBD in a subject" (Reply entered 11/15/05, p.8, para 3).*

Contrary to applicant's statement, the instant claims are not drawn to a method of diagnosing IBD in a subject. The instant claims recite a method of determining the expression level of genes from cells of a given tissue type.

*Applicants argue that the rejections over the combination of Dieckgraefe and Poulakkainen references do not teach any of the claimed genes in the instant Claims (i.e., GRO3, HNL, elafin, or COL6A3) (Reply entered 11/15/05, p. 8, para 4).*

The instant claims (Claim 42) lists five specific genes including GRO3, HNL, elafin, or COL6A3, and MMP-12, which the MMP-12 gene is the elected species of gene as discussed supra in the Election/Restrictions section of the instant Office action. As discussed above and pointed out by the applicants (Reply entered 11/15/05, p. 7, para 2), Puolakkainen et al teach MMP-12 gene is differentially expressed in IBD cells.

16. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol 114, No. 4, April 1998; previously cited) and in view of the instant specification disclosure. This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

**Dieckgraefe et al**, throughout the publication, disclose a method for identifying gene expressed in IBD as discussed supra.

Dieckgraefe et al do not explicitly teach the genes listed in the instant Claim 42.

However, the instant specification discloses that 'Table 1 indicates those sequences which are over- or under expressed in a CD- or UC-derived cells relative to normal tissue' (see specification page 19, lines 6-7), and further provides gene accession numbers of the genes (thus the genes are publicly available). Thus a person of ordinary skill in the art would at the time the invention was made would have been motivated to use the method of Dieckgraefe et al and the

Art Unit: 1639

known genes in determining the differential expressed genes in IBD. All the genes used in the claimed method are well known in the art.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use the well known genes (all these genes are known to have a role in IBD such as the ones involved in host defense) in the method taught by Dieckgraefe et al, because Dieckgraefe et al teach the need to identify gene markers differentially expressed in different diseases such as UC and CD for potential pharmaceutical purposes, and many host defense molecules are over expressed in IBD.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for monitoring gene expression such as using DNA microarray and the specific genes (such as MMP-12) are known in the prior art such as taught by Dieckgraefe et al and the instant specification.

*Discussion and Answer to Argument*

17. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue that the instant claims (especially Claim 42) "recites a method for diagnosing IBD in a subject" (Reply entered 11/15/05, pp.8-9, bridging para). Applicants also argue that the genes listed in Table 1 (including GRO3, HNL, elafin, or COL6A3, and MMP-12)*

Art Unit: 1639

*of the instant specification are not known for their roles in IBD (Reply entered 11/15/05, p. 9, para 2).*

Contrary to applicant's assertion, the instant specification discloses that "Among these, IBD hallmarks, such as cytokine members...MMPs and..." (p. 6, last para of the instant specification). Thus, the instant specification discloses that MMPs (including MMP-12) are "hallmarks" of IBD as known in the art at the time the invention was made.

Furthermore, contrary to applicant's statement, the instant claims are not drawn to a method of diagnosing IBD in a subject. The instant claims recite a method of determining the expression level of genes from cells of a given tissue type, and then compare the expression levels from the said cells and control cells. The instant claimed invention does not require that the genes are known for their specific roles in IBD.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

Art Unit: 1639

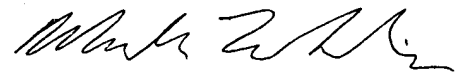
however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL  
Art Unit 1639  
10/11/2006

  
MARK SHIBUYA, PH.D.  
PATENT EXAMINER